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09/656,915	09/07/2000	Larry I. Benowitz	CMZ-129	2385

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EXAMINER

NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/656,915

**Applicant(s)**

BENOWITZ, LARRY I.

**Examiner**

Christopher J Nichols, Ph.D.

**Art Unit**

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 3 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-57 is/are pending in the application.
- 4a) Of the above claim(s) 1-29 and 39-57 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 30-38 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-57 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 September 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election without traverse of Group V (claims 30-38) in the Response filed 3 February 2004 is acknowledged. Claims **1-29** and **39-57** are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

### ***Sequence Rules***

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein. This application discloses two amino acid sequences in Figure 2 but only one SEQ ID NO. Applicant may include the second SEQ ID NO in the Figure legend in the Specification to remedy this objection. Correction is required.

### ***Claim Objections***

3. Claim **35** is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 35 reiterates the goal of the preamble to "identify a compound that modulates axonal outgrowth of a central nervous system neuron" without further limiting the original scope of the parent claim.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 30-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an in vitro method for identifying a compound that modulates N-kinase dependent phosphorylation of a substrate comprising contacting N-kinase with a test compound and determining the ability of the test compound to increase or decrease N-kinase dependent phosphorylation of a substrate*, does not reasonably provide enablement for *an in vivo method for identifying a compound that modulates axonal outgrowth of a central nervous system neuron or assaying other as of yet identified activities such as axonal outgrowth of a central nervous system neuron*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.
5. The claims are drawn very broadly to methods of identifying a compound that modulates axonal outgrowth of a central nervous system neuron. The language of said claims encompasses both *in vivo* and *in vitro* assays, as delineated in the Specification (pp. 8 lines 20-24).
6. The specification teaches an *in vitro* method for identifying a compound that inhibits or enhances N-kinase dependent phosphorylation of a substrate.

Art Unit: 1647

7. However, the specification fails to provide any guidance for the successful use or practice of a method for identifying compounds with modulate K-kinase dependent phosphorylation of a substrate *in vivo*. Since resolution of the various complications in regards to measuring the phosphorylation of a substrate by N-kinase in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with known N-kinase signs and products of N-kinase dependent phosphorylation to correlate with changes *in vivo*. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

8. Additionally, a person skilled in the art would recognize that predicting the efficacy of practicing the method *in vivo* based solely on its performance *prophetic guidance* as highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* assays, such a disclosure would not be considered enabling since the state of central nervous system and its cells are highly unpredictable. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;

Art Unit: 1647

- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

9. The following references are cited herein to illustrate the state of the art of N-kinase and central nervous system neurons.

10. On the breadth of the claims, the Specification does not teach how a N-kinase phosphorylated substrate would be identified or distinguished from any one of the several hundred known kinases *in vivo* {see Bossemeyer (1995) "Protein Kinases—structure and function." FEBS Letters **369**: 57-61}.

11. On the nature of the invention, US 6,001,583 (14 December 1999) Margolis teaches that kinases fall into one of three classes, serine, threonine, and tyrosine kinases. Overall kinases represent a large family of proteins and include many growth factor receptors (Col. 1 lines 35-67; Col. 2 lines 33-50). However, the Specification is silent on how the skilled artisan would untangle the web of secondary messenger cascades that kinases, such as Protein Kinase A and Protein Kinase C as well as N-kinase, are intertwined with as to differentiate the phosphorylated products and correctly assign any changes to N-kinase {see Kandel *et al.* (2000) Principles of Neural Science (4<sup>th</sup> Ed.) Chapter 13 "Modulation of Synaptic Transmission: Second Messengers" pp. 229-252}.

12. On the state of the prior art, Rowland-Gangé & Greene (February 1990) "Multiple Pathways of N-Kinase Activation in PC12 Cells." Journal of Neurochemistry **54**(2): 424-433 (IDS#CA) teach that N-kinase is stimulated by a myriad of growth factors, is widely distributed, and is involved in a number of secondary messenger pathways (pp. 432-433). Taking this into

Art Unit: 1647

consideration, the Specification does not provide guidance on how to determine N-kinase activity *in vivo*, in an animal model for instance, due to the complexity of N-kinases functions. Therefore outside an environment, such as a cell-based or cell-free *in vitro* system where such factors may be easily controlled, the skilled artisan is confronted with an undue burden of experimentation to develop an effective system to carry out the invention *in vivo*.

13. Furthermore no nexus is present in the Specification or the prior art to show that N-kinase is necessary or sufficient to affect axonal outgrowth of a central nervous system neuron. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* screening methods as exemplified in the references herein.

14. Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "modulates" in claim 30 is a relative term which renders the claim indefinite. The term "modulates" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Neither the prior art nor the Specification clearly and unambiguously defines "modulates". For instance the American Heritage® Dictionary of the English Language (2000) defines modulate as "To adjust or adapt to a certain proportion; regulate or temper" but does not specify to which degree, to what extent, nor what parameters are changed, or what amount thereof.

Art Unit: 1647

15. Claims **30-37** are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the N-kinase activity except for phosphorylation of a substrate which are measured by the claims and how said activity is measured.

***Summary***

16. No claims are allowed.



Art Unit: 1647

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

*Elizabeth C. Kemmerer*

CJN  
April 6, 2004

**ELIZABETH KEMMERER  
PRIMARY EXAMINER**